DIPHTHERIA
Report Immediately

✓DISEASE AND EPIDEMIOLOGY

Clinical Description:

Respiratory (toxigenic strains):

Respiratory (nasal, pharyngeal, tonsillar, and laryngeal) diphtheria is typically caused by toxin-producing (toxigenic) strains of *C. diphtheriae.* The respiratory form of the disease is characterized by the presence of a membrane that is usually visible over the tonsils or the throat. The membrane is not easy to remove. Initial symptoms of illness include a sore throat and low-grade fever. Swelling of the neck ("bullneck") from soft-tissue inflammation can develop and is a sign of severe disease. The membrane may obstruct breathing and can be life threatening. Complications of diphtheria include myocarditis (inflammation of the heart) and nerve paralysis. The respiratory form of diphtheria usually lasts several days, and complications can persist for months.

Respiratory (non-toxigenic strains):

Nontoxigenic *C. diphtheriae* can also cause membranous pharyngitis; the disease is usually mild but can lead to endocarditis. The isolation of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. Although the frequency with which this occurs is unknown, a small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria.

Cutaneous:

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains, is usually mild, typically consisting of nondistinctive sores or shallow ulcers, and only rarely involving toxic complications (1–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

Causative Agent:

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae*, a pleiomorphic, gram-positive, irregularly staining bacterium. Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. psuedotuberculosis*) may produce diphtheria toxin and can cause classic diphtheria. Whether diphtheria bacteria produce toxin depends on infection by a virus bacteriophage carrying the *tox* gene. There are four strains or biotypes of *C. diphtheriae:* gravis, mitis, intermedius, and belfanti. Toxin-producing strains of all biotypes produce an identical exotoxin. There is no consistent difference in pathogenicity or severity of disease among the biotypes; however, the order of their likelihood of producing toxin is: gravis, mitis, intermedius, and belfanti.

Differential Diagnosis:

The primary diagnostic concern is to differentiate diphtheria from *Corynebacterium ulcerans*. This causes a disease that is clinically similar to *C. diphtheriae*. *C. ulcerans* is a zoonotic illness that can be transmitted from dairy animals and other pets. *C. ulcerans* is usually milder, but at least one report has identified *C. diphtheriae* toxins carried by *C. ulcerans.*

Other pathogens can cause membranes in the respiratory tract, including *Streptococcus* species, Epstein-Barr virus, cytomegalovirus, *Candida,* and anaerobic organisms (Vincent's angina).

Laboratory identification:

If diphtheria is strongly clinically suspected, treatment should begin prior to laboratory confirmation. However, laboratory diagnosis is essential for public health purposes.

Serology:

Serologic results do not provide a clear diagnostic answer; therefore, serology is not the preferred method for diagnosis.

Culture:

Bacteriological culture is essential for determining biotype and toxigenicity of the diphtheria isolate. A clinical specimen for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. Specimens should be taken from the nose and throat and from the membrane. If possible, swabs also should be taken from beneath the membrane. After *C. diphtheriae* has been isolated, the biotype (substrain) should be determined. Only large reference laboratories are likely to be capable of culturing diphtheria. Because special media are required, laboratory personnel should be notified if *C. diphtheriae* is suspected. However, because isolation of *C. diphtheriae* is not always possible (many patients have already received several days of antibiotics by the time a diphtheria diagnosis is considered) and because of the extended time required for the test, PCR testing should always be performed for a faster result. For additional information on the collection of specimens for diphtheria testing, please see **Appendix 1: Collection of Specimens for Isolation of *C. diphtheria*** from the *CDC's Manual for the Surveillance of Vaccine-Preventable Diseases* http://www.cdc.gov/vaccines/pubs/surv-manual/default.htm.

PCR:

Specimens for PCR should always be collected at the same time as specimens for culture. Because isolation of *C. diphtheriae* is not always possible (many patients have already received several days of antibiotics by the time a diphtheria diagnosis is considered), PCR can provide additional supportive evidence for the diagnosis of diphtheria. PCR should not be used as a replacement of culture.

Treatment:

If diphtheria is suspected, diphtheria antitoxin should be administered, even before laboratory confirmation. Antitoxin is available through the CDC and requires an approval process for distribution. The Utah Department of Health will assist with this process.

A test for sensitivity to diphtheria antitoxin should be carried out each time diphtheria antitoxin is administered. The recommended dosage and route of administration depend

on the extent and duration of disease. Antitoxin is only available through an investigational new drug protocol through the CDC. Antibiotics are not a substitute for antitoxin. For more detailed information on antitoxin sensitivity testing and administration, please see the CDC's **Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases**.

Procaine penicillin G (IM) (25,000 to 50,000 units/kg/day for children and 1.2 million units/kg/day for adults, in 2 divided doses) or parenteral erythromycin (40-50 mg/kg/day, with a maximum of 2 grams/day) has been recommended until the patient can swallow comfortably, at which point erythromycin PO in 4 divided doses or penicillin V PO (125-250 mg 4 times daily) may be substituted for a recommended total treatment period of 14 days. Some erythromycin resistant strains have been identified, but they are uncommon and not a public health problem. Newer macrolide antibiotics, including azithromycin and clarithromycin, do not offer any substantial advantage over erythromycin.

Case fatality:

Respiratory: The case fatality rate of 5–10% for respiratory diphtheria has changed little in 50 years. In recent epidemics in the former Soviet Union, the case-fatality ratio ranged from 3–23%.

Reservoir:

Humans are the only host of *C. diphtheriae*.

Transmission:

Diphtheria is transmitted from person to person by respiratory droplets or by direct contact with the nasopharyngeal secretions of an infected person. Contact with articles soiled with discharges from cutaneous lesions of infected people can be a source of infection, but this has rarely been documented. Raw milk has served as a vehicle for transmission. Asymptomatic carriers are important in sustaining transmission.

Incubation period:

Respiratory diphtheria begins 2–7 days after infection.

Period of communicability:

In untreated persons, the infectious period begins at symptom onset and extends through two weeks after onset in the majority of patients (but may range up to six weeks post onset). If patients are treated with antibiotics, communicability usually lasts less than four days. However, chronic carriage may occur, even after antimicrobial therapy. Patients are considered infectious until 2 successive nose and throat cultures (and cultures of skin lesions in cutaneous diphtheria), obtained ≥24 hours apart and at least 24 hours after completion of antimicrobial therapy, are negative.

Susceptibility:
Infants born to immune mothers have passive protection, which is usually lost before the 6th month. Disease or inapparent infection usually, but not always, induced lifelong immunity. More than 40% of adults lack protective levels of circulating antitoxin.

Epidemiology:
Infection can occur in immunized, partially immunized, and unimmunized persons. However, disease is usually less severe in those who are partially or fully immunized. Diphtheria is endemic in many parts of the world, including countries of the Caribbean and Latin America. The incidence of respiratory diphtheria is greatest in the fall and winter, but summer epidemics may occur in warm moist climates in which skin infections are prevalent.

Most cases of diphtheria reported recently in the U.S. were related to importation. The last known case in Utah occurred in 1960. The last non-imported case in the U.S. was in 2000. Currently, diphtheria is circulating in Russia and surrounding former USSR countries. It is estimated that more than 40% of U.S. adults lack protective levels of circulating antitoxin.

C. ulcerans infection in humans frequently has been associated with antecedent contact with farm animals or with consumption of unpasteurized dairy products; human-to-human transmission has not been documented

✓PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:
- Immediately contact the epidemiology program at the Utah Department of Health for assistance with obtaining laboratory confirmation and antitoxin.
- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention, and to alert them to any events of disease circulation.
- Assure early and appropriate treatment with diphtheria antitoxin and antibiotics.
- Assure appropriate laboratory confirmation is performed.
- Recommend routine immunization against diphtheria.
- Identify clusters or outbreaks of this disease.
- Identify and evaluate contacts, and provide necessary antimicrobial prophylaxis to prevent further spread of the disease.

Prevention:
The most effective control is widespread active immunization with diphtheria toxoid.

Chemoprophylaxis:
Close contacts should be given (preferably) a 7-10 day course of erythromycin (PO, 40 mg/kg/day for children and 1 gram/day for adults) or a single dose of benzathine

penicillin (IM) (600,000 units for persons under 6 years and 1.2 million units for persons 6 or older). If close contacts are culture positive, treat them as patients, not contacts. Household contacts should be prophylaxed **REGARDLESS** of immunization status.

Vaccine:

Diphtheria vaccine is complexed with acellular pertussis and tetanus toxoid, also known as DTaP. Immunization should be initiated in infancy. The first 3 doses are given at 4-8 week intervals beginning at 6-8 weeks of age; a fourth dose should be 6-12 months after the third dose; and a fifth dose given at 4-6 years of age, but prior to school entry. This dose is not necessary if the fourth dose is given at 4 years or later.

Adults should receive vaccine specifically formulated with reduced concentration of diphtheria toxoid (Tdap). Active protection for adults should be maintained by administration of this vaccine every 10 years.

Isolation and quarantine requirements:

Isolation: Non-hospitalized patients with respiratory diphtheria, caused by toxigenic or non-toxigenic strains, and non-hospitalized patients with cutaneous diphtheria, caused by toxigenic strains, should be voluntarily isolated in their house until proven to be culture negative.

Hospital: In addition to standard precautions, use droplet precautions for respiratory diphtheria, and contact precautions for cutaneous diphtheria. Isolation measures should be continued until 2 negative cultures from both nose and throat are obtained (not less than 24 hours apart and not less than 24 hours after completion of antibiotic therapy). When culture is impractical, isolation may end following 14 days of appropriate antibiotic therapy.

Quarantine: Adult contacts whose occupations involve handling food (especially milk) or close association with non-immunized children should be excluded from work until treated and bacteriological examinations prove them not to be cases or carriers.

✓CASE INVESTIGATION

Reporting:

All suspected and confirmed cases of diphtheria should be immediately reported to public health.

Case definition:

Diphtheria (*Corynebacterium diphtheriae*) (1995):

Clinical Description

An upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory Criteria

- Isolation of *Corynebacterium diphtheriae* from a clinical specimen, or
- Histopathologic diagnosis of diphtheria

Case Classification

Probable: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.
Confirmed: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

Comments

Cutaneous diphtheria and respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheria isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC. Rarely, respiratory diphtheria may result from infection with other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*). These isolates should also be forwarded to the CDC.

Case Investigation Process:

All highly suspect cases (including cutaneous) of diphtheria warrant immediate action until they are shown not to be caused by toxigenic *C. diphtheriae*. Cases or carriers of toxigenic *C. diphtheriae* should be managed as follows:

- Local and state health departments and CDC should be immediately notified.
- Appropriate laboratory samples and preliminary clinical and epidemiologic information (including vaccine history) should be obtained.
- Presumptive treatment with antibiotics and antitoxin should be started.
- Strict isolation should be imposed until at least two cultures are negative 24 hours after antibiotics were discontinued.
- All case contacts should be identified and appropriately managed (explained in detail below).
- If case is not imported, the source of infection the source of infection should be identified.

Outbreaks:

A single case of diphtheria without any travel history will be considered an outbreak. Identify all close contacts and define population groups at specific risk and immunize. An epidemiologically linked case is one in which the patient has had contact with one or more persons who have or had the disease, and transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

Identification of case contacts:

Close contacts are defined as persons who have been within 3 feet (large droplet range) of the patient. This would typically include household members, persons who shared food, drink, or eating/drinking utensils with the patient, and health care workers in contact with the patient's oral or respiratory secretions. Contacts that were in brief contact with the case but who do not meet the definition for close contact are not considered significant contacts.

Case (close) contact management:

Close contact management is necessary for all cases of respiratory diphtheria, caused by toxigenic or non-toxigenic strains, and cutaneous diphtheria, caused by toxigenic strains.

- All close contacts should have cultures taken from their nose and throat and be kept under active surveillance for 7 days, regardless of vaccination history.
- After culture, all close contacts should receive antibiotic prophylaxis.
- Previously immunized contacts should receive a booster dose of diphtheria toxoid if more than 5 years have elapsed since their last dose, and a primary series should be initiated in non-immunized contacts.
- Adult contacts whose occupations involve handling food (especially milk) or close association with non-immunized children should be immediately excluded from work until treated and culture results are negative.
- Treat any confirmed carrier with an adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks to ensure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin and should submit samples for follow-up cultures.
- Contact tracing of cases with non-toxigenic cutaneous diphtheria is not necessary.

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